

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204623Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 204623

SUPPL # NA

HFD # 170

Trade Name Pennsaid

Generic Name diclofenac sodium topical solution, 2% w/w

Applicant Name Mallinckrodt Inc.

Approval Date January 16, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 020142	Cataflam (diclofenac potassium)
NDA# 021234	Flector (diclofenac epolamine)
NDA# 022202	Zipsor (diclofenac potassium)
NDA# 022165	Cambia (diclofenac potassium)
NDA# 021005	Solaraze (diclofenac sodium)
NDA# 022122	Voltaren (diclofenac sodium)
NDA# 19201	Voltaren (diclofenac sodium)
NDA# 20254	Voltaren -XR(diclofenac sodium)
NDA# 204592	Zorvolex (diclofenac)
NDA# 020947	Pennsaid (diclofenac sodium)

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Trial COV05100031 was a Phase 2, 4-week, 2-arm, double-blind, vehicle-controlled, parallel group, randomized trial designed to characterize the analgesic effect and determine the effect size of PENNSAID 2% topical solution, to determine if an effective level of analgesia was maintained throughout the 12-hour dosing interval, and to evaluate the safety of PENNSAID 2% topical solution in the treatment of OA of the knee.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously

approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Trial COV05100031 was a Phase 2, 4-week, 2-arm, double-blind, vehicle-controlled, parallel group, randomized trial designed to characterize the analgesic effect and determine the effect size of PENNSAID 2% topical solution, to determine if an effective level of analgesia was maintained throughout the 12-hour dosing interval, and to evaluate the safety of PENNSAID 2% topical solution in the treatment of OA of the knee.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 075045 YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES ! NO
Explain: ! Explain:

Investigation #2 !
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Mavis Darkwah, PharmD
Title: Regulatory Project Manager, HFD-170
Date: December 23, 2013

Name of Office/Division Director signing form: Sharon Hertz, MD
Title: Deputy Director, HFD-170

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

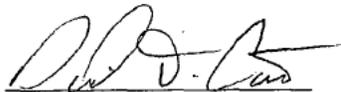
MAVIS Y DARKWAH
01/16/2014

SHARON H HERTZ
01/16/2014

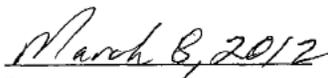
CERTIFICATION REQUIRED BY
GENERIC DRUG ENFORCEMENT ACT OF 1992

Pursuant to Section 306(k) of the Federal Food, Drug and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992, Mallinckrodt Inc. hereby certifies that Mallinckrodt did not and will not use, in any capacity, the services of any person debarred under subsection (a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application for PENNSAID (diclofenac sodium topical solution) 2% w/w.

Mallinckrodt Inc. Certifies further that, during the previous five years, it has not sustained a conviction that is described in subsections (a) or (b) of the Generic Drug Enforcement Act of 1992. In addition, no person affiliated with Mallinckrodt Inc. that was responsible for the development or submission of this application has been convicted of an offense described in subsections (a) or (b) of the Generic Drug Enforcement Act of 1992.



David J. Cano
Interim Vice President, Global Human Resources



Date

505(b)(2) ASSESSMENT

Application Information		
NDA # 204623	NDA Supplement #:	Efficacy Supplement Type SE-
Proprietary Name: Pennsaid Established/Proper Name: diclofenac sodium topical solution 2% w/w Dosage Form: topical solution, <u>metered</u> (<i>this change required it to be a new NDA[new dosage form] and not an efficacy supplement under NDA 020947</i>) Strengths: 2%		
Applicant: Mallinckrodt Inc.		
Date of Receipt: May 5, 2012/August 7, 2013 (first cycle / second cycle)		
PDUFA Goal Date: March 4, 2013/February 7, 2014		Action Goal Date (if different): March 4, 2013/ January 16, 2014
Proposed Indication(s): to treat pain of osteoarthritis of the knee(s)		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Published literature	Includes pharmacology, nonclinical pharmacokinetics, and toxicology literature reviews
Voltaren (diclofenac sodium) delayed release oral tablets 75 mg, NDA 019201	clinical pharmacology information including distribution, metabolism and excretion

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

In the original submission, the Applicant conducted relative bioavailability studies with Pennsaid 1.5% solution, oral diclofenac tablets, and the proposed Pennsaid 2% solution for bridging purposes under Study COV05100070 and another study comparing the two formulations of Pennsaid under Study COV05100175.

Initially, we thought the PK data may be may be sufficient to support approval, and as a result, request OSI inspect the clinical pharmacology study site. OSI found the site failed to retain samples of the study drug tested and, therefore, recommended that the studies not be relied upon to support the application.

Currently, we have determined that the efficacy will be supported by a 4-week efficacy study and the PK study would just be supportive. In this setting we would not have requested an inspection of the clinical pharmacology site, but now that we already have the information. Considering that the OSI inspection results were unacceptable, the study results could not be used to support the NDA application. Therefore, complete response was given to the sponsor in the first cycle, even if the relative bioavailability studies were finally determined as not pivotal. Based on the recommendation from the 505(b)(2) committee, an oral Voltaren arm in the relative BA study is not needed. The sponsor was asked in the complete response letter to conduct a new relative bioavailability study using proposed diclofenac sodium topical solution, 2% and PENNSAID 1.5%..

In the re-submission, the sponsor re-conducted the relative bioavailability study between proposed 2% and PENNSAID 1.5%. Based on the study results, it is concluded that diclofenac AUC0-12 and Cmax value from 2% topical solution at

steady state were 49% and 46% higher compared to those from PENNSAID 1.5% topical solution, respectively, at steady state on Day 8, and they are much lower compared to those from oral diclofenac tablet (e.g. Voltaren 75 mg, NDA 019201).

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO," proceed to question #5.

If "YES," list the listed drug(s) identified by name and answer question #4I.

I Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Voltaren (diclofenac sodium) delayed release oral tablets 75 mg	NDA 019201	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing: Voltaren (diclofenac sodium)
delayed release oral tablets 75 mg, NDA 019201

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for change in dosage form, from solution to metered solution, a change in concentration from 1.5% to 2% and a new dosing regimen from QID to BID.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "**NO**" to (a) proceed to question #11.
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
YES NO

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
YES NO

If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):
Solaraze Topical Gel (NDA 21005)
Voltaren Topical Gel (NDA 22122)
Voltaren Ophthalmic Solution (NDA 20037) + generics
Pennsaid Topical Solution (NDA 20947)
generic delayed release tablets
Voltaren XR Tablets (NDA 20254) + generics

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): **The applicant claims a certification of no relevant patents (21 CFR 314.50(i)(1)(II), but they have provided form 3542a and referenced 8217078. A search in Orange book, for Pennsaid revealed unexpired patent 8217078. The Patent is for method of use. The applicant owns the patent, which expires July 10, 2029.**

No patents listed *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAVIS Y DARKWAH
01/16/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 204623	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: Pennsaid Established/Proper Name: diclofenac sodium 2% topical solution Dosage Form: Solution		Applicant: Mallinkrodt Inc Agent for Applicant (if applicable): N/A
RPM: Mavis Darkwah, PharmD, Regulatory Project Manager		Division: Division of Anesthesia, Analgesia, and Addiction Products

<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): NDA 019201, Voltaren Tablets, 75mg</p> <p>Provide a brief explanation of how this product is different from the listed drug. This is a solution, as compared to tablet or gel</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input checked="" type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
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<p>❖ Actions</p> <ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>February 7, 2014, but action taken early on January 16, 2014</u> • Previous actions (<i>specify type and date for each action taken</i>) 	<p><input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR</p> <p>Complete Response on 03/04/2013</p>
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¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC <input type="checkbox"/> Breakthrough Therapy designation</p> <p>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p>REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input checked="" type="checkbox"/> MedGuide w/o REMS <input checked="" type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<p><input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other</p>

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	✓
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	✓ Action(s) and date(s) ✓ CR: 03/04/2013 ✓ AP: 01/16/2014
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	✓ 01/13/2014
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	✓ Aug. 7, 2013
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	12/23/2013
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	08/07/2013
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • <i>Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</i> 	Carol A. Holquist, letter accepting proposed name, 10/07/2013; Vicky Borders-Hemphill; Jamie Wilkins Parker review confirming name still acceptable 10/07/2013
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM Mavis Darkwah S. Patwardhan 07/17/2012 <input checked="" type="checkbox"/> DMEPA V. Borders-Hemphill, Morgan Walker, C. Holquist; Review, 10/24/13, 12/18/213 <input checked="" type="checkbox"/> DMPP/PLT 12/05/2012 02/22/2013 <input checked="" type="checkbox"/> OPDP (DDMAC) Eunice Chung-Davies, Review, 11/27/2013 M. Darkwah, Consult Request form, 09/26/13 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	505(b)(2) Assessment; cleared by committee on 03/06/2013, and confirmed as still acceptable on 12/10/13) <u>Filing reviews letter:</u> July 17, 2012 <input type="checkbox"/> Not a (b)(2) <input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC Jan. 30, 2013 If PeRC review not necessary, explain: _____ Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> Regulatory Briefing (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg Sep. 25, 2006
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	Pre-IND Aug. 28, 2008, End of Review: April 25, 2013
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 48-hour alert or minutes, if available (<i>do not include transcript</i>) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None March 4, 2013
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None Feb. 11, 2013
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁶	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	Feb. 11, 2013
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	Jan. 28, 2013
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None

⁶ Filing reviews should be filed with the discipline reviews.

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	01/28/2013 in Clinical Primary review and Deputy Division Director's review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested Nov. 19, 2012
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Jan. 28, 2013
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Jan. 28, 2013, Feb. 26, 2013(addendum), Nov. 16, 2013
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None Jan. 28, 2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/> None requested Dec. 19, 2012

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None Feb. 1, 2013, Feb. 8, 2013
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	Feb. 1, 2013
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report). <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>	Date completed: Feb. 1, 2013 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹				
NDA # 204623 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:		
Proprietary Name: Pennsaid ^{(b) (4)} Established/Proper Name: diclofenac sodium Dosage Form: topical solution, metered		Applicant: Mallinckrodt Inc. Agent for Applicant (if applicable):		
RPM: Swati Patwardhan		Division:		
<table style="width: 100%; border: none;"> <tr> <td style="width: 45%; vertical-align: top; padding: 5px;"> <p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p> </td> <td style="width: 55%; vertical-align: top; padding: 5px;"> <p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Voltaren (diclofenac sodium) delayed release oral tablets 75 mg, NDA 019201</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>Different dosage form, Voltaren is oral tablets, where a Pennsaid is a topical solution</p> <p><input checked="" type="checkbox"/> This application does not rely upon a listed drug. <input checked="" type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> </td> </tr> </table>			<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Voltaren (diclofenac sodium) delayed release oral tablets 75 mg, NDA 019201</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>Different dosage form, Voltaren is oral tablets, where a Pennsaid is a topical solution</p> <p><input checked="" type="checkbox"/> This application does not rely upon a listed drug. <input checked="" type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Voltaren (diclofenac sodium) delayed release oral tablets 75 mg, NDA 019201</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>Different dosage form, Voltaren is oral tablets, where a Pennsaid is a topical solution</p> <p><input checked="" type="checkbox"/> This application does not rely upon a listed drug. <input checked="" type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>			
<table style="width: 100%; border: none;"> <tr> <td style="width: 70%; vertical-align: top; padding: 5px;"> <p>❖ Actions</p> <ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is March 4, 2013 • Previous actions (<i>specify type and date for each action taken</i>) </td> <td style="width: 30%; vertical-align: top; padding: 5px;"> <p><input type="checkbox"/> AP <input type="checkbox"/> TA <input checked="" type="checkbox"/> CR</p> <p><input checked="" type="checkbox"/> None</p> </td> </tr> </table>			<p>❖ Actions</p> <ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is March 4, 2013 • Previous actions (<i>specify type and date for each action taken</i>) 	<p><input type="checkbox"/> AP <input type="checkbox"/> TA <input checked="" type="checkbox"/> CR</p> <p><input checked="" type="checkbox"/> None</p>
<p>❖ Actions</p> <ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is March 4, 2013 • Previous actions (<i>specify type and date for each action taken</i>) 	<p><input type="checkbox"/> AP <input type="checkbox"/> TA <input checked="" type="checkbox"/> CR</p> <p><input checked="" type="checkbox"/> None</p>			

¹The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists documents to be included in the Action Package.

²For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Breakthrough Therapy designation </p> <p> <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input checked="" type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)). 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For each **paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>CONTENTS OF ACTION PACKAGE</p>	
<p>❖ Copy of this Action Package Checklist⁴</p>	<p>✓</p>
<p>Officer/Employee List</p>	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input type="checkbox"/> Included</p>
<p>Action Letters</p>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) CR- March 4, 2013</p>
<p>Labeling</p>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	<p>✓</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>✓</p>
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	<input checked="" type="checkbox"/>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/>
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/>
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	NA (Withdrawn)
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM July 17, 2012 <input checked="" type="checkbox"/> DMEPA Dec. 18, 2012 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) Feb. 22, 2013 <input checked="" type="checkbox"/> OPDP (DDMAC) Feb. 22, 2013 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	July 17, 2012
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input type="checkbox"/> Not a (b)(2) March 6, 2013
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input type="checkbox"/> Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FD RR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	✓
❖ Internal memoranda, telecons, etc.	✓
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg
• EOP2 meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg Sep. 25, 2006
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	Pre-IND Aug. 28, 2008, End of Review: April 25, 2013
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None March 4, 2013
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None Feb. 11, 2013
PMR/PMC Development Templates <i>(indicate total number)</i>	<input checked="" type="checkbox"/> None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	
• Clinical review(s) <i>(indicate date for each review)</i>	Jan. 28, 2013
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and REMS Supporting Document <i>(indicate date(s) of submission(s))</i>	
• REMS Memo(s) and letter(s) <i>(indicate date(s))</i>	
• Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i>	<input checked="" type="checkbox"/> None

⁶ Filing reviews should be filed with the discipline reviews.

❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	<input type="checkbox"/> None requested Nov. 19, 2012
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None Jan. 28, 2013
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None Jan. 28, 2013, Feb. 26, 2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page 25
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input type="checkbox"/> None requested Dec. 19, 2012
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None Feb. 8, 2013
❖ Microbiology Reviews	<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Feb. 8, 2013
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <u>NOT</u> include EER Detailed Report) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: Jan. 31, 2013 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

Darkwah, Mavis

From: Bierman, Bunny <Bunny.Bierman@mallinckrodt.com>
Sent: Monday, January 13, 2014 2:50 PM
To: Darkwah, Mavis
Subject: RE: Labeling-NDA 204623
Attachments: NDA 204623 PI FDA Comment 23Dec13_MNK response.doc; NDA 204623 PI FDA Comment 23Dec13_MNK clean.doc

Dear Mavis,

Per our phone conversation, we accept the label (prescribing information, medication guide and instructions for use) proposed by the Division in the Dec 23rd email.

In addition, minor two minor editorial/ formatting errors were corrected on Page 1 and 4 in the attached (track-changes and clean) version of the prescribing information.

Please let me know if there are any additional questions.

Thank you,
Bunny

From: Darkwah, Mavis [mailto:Mavis.Darkwah@fda.hhs.gov]
Sent: Monday, December 23, 2013 8:21 AM
To: Bierman, Bunny
Subject: RE: Labeling-NDA 204623

Dear Bunny,

Additional internal labeling review has resulted in a determination that the use of (b) (4) in the package insert and medication guide is incompatible with the approved proprietary name of "PENNSAID." We have therefore revised these documents to remove the (b) (4) modifier. No other changes have been made, other than minor editorial changes to the Medication Guide.

Attached please find the word versions of the label, Medication Guide (MG), and Instructions for Use (IFU) with our proposed changes. Please return a version of these labels with our changes accepted and with your proposed changes tracked. Also provide a clean copy of the word version.

We request a response as soon as possible.

Please contact me if there are any questions.

Regards,

Mavis

*Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
FDA/CDER/OND/ODE II*

Ph: (240) 402-3158

Email: Mavis.Darkwah@fda.hhs.gov

From: Bierman, Bunny [<mailto:Bunny.Bierman@mallinckrodt.com>]

Sent: Monday, December 16, 2013 9:04 PM

To: Darkwah, Mavis

Subject: RE: Labeling-NDA 204623

Thank you for the email.

Bunny

From: Darkwah, Mavis [<mailto:Mavis.Darkwah@fda.hhs.gov>]

Sent: Monday, December 16, 2013 3:37 PM

To: Bierman, Bunny

Subject: RE: Labeling-NDA 204623

Dear Bunny,

The Division accepts your proposed change (Section 2.2).

Regards,

Mavis

From: Bierman, Bunny [<mailto:Bunny.Bierman@mallinckrodt.com>]

Sent: Thursday, December 12, 2013 4:53 PM

To: Darkwah, Mavis

Subject: RE: Labeling-NDA 204623

Dear Mavis,

Please find attached word versions, both clean and changes tracked, with our response to the proposed changes to the label.

Thank you for your time,

Bunny

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Sent: Wednesday, December 11, 2013 2:11 PM

To: Bierman, Bunny

Subject: RE: Labeling-NDA 204623

Importance: High

Dear Bunny,

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We request a response as soon as possible, no later than close of business Thursday, December 12, 2013.

Let me know if there are any questions.

Regards,

Mavis

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Dear Mavis,

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If there are any questions, please feel free to contact me directly. Thanks for your time.

Bunny

From: Darkwah, Mavis [<mailto:Mavis.Darkwah@fda.hhs.gov>]
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To: Bierman, Bunny
Subject: RE: Labeling-NDA 204623

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Thank you for your time on this and hope you have a nice holiday break.

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Sent: Monday, November 25, 2013 12:31 PM
To: Bierman, Bunny
Subject: RE: Labeling-NDA 204623

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Thanks very much for your time,
Bunny

Bunny Bierman | Regulatory Affairs Manager
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We request a response preferably by close of business Friday November 15, 2013.

Regards,

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Importance: High

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Bunny

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Sent: Monday, November 25, 2013 12:31 PM
To: Bierman, Bunny
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Mavis

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Thanks very much for your time,
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18 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Darkwah, Mavis

From: Darkwah, Mavis
Sent: Thursday, December 12, 2013 8:10 AM
To: 'Bierman, Bunny'
Subject: RE: Labeling-NDA 204623
Attachments: NDA 204623 MG & IFU FDA comments 12Dec13.doc

Bunny,

Thank you for alerting me to this error. Please find attached the word version of the Medication Guide (MG), and Instructions for Use (IFU) with our proposed changes. Although you previously accepted our changes, please return a version with our changes accepted and with your proposed changes tracked. Also provide a clean copy of the word version.

Regards,

Mavis

From: Bierman, Bunny [mailto:Bunny.Bierman@mallinckrodt.com]
Sent: Wednesday, December 11, 2013 6:00 PM
To: Darkwah, Mavis
Subject: RE: Labeling-NDA 204623
Importance: High

Mavis,

In the meantime, I have a follow-up question. We just noticed a small error in the recent IFU revision that occurred during the recent round of FDA revisions (Dec 06 2013). Please see the second to last bullet point, on the last page of the IFU (provided below also). I believe a bullet may have been removed inadvertently. I've reattached the supporting documents from Dec 06 your reference.
Thank you

- exercise following application of PENNSAID ^(b) use sunlamp and tanning beds. Protect your treated knee from sunlight. Wear clothes that cover your skin if you have to be in the sunlight.

From: Bierman, Bunny
Sent: Wednesday, December 11, 2013 3:03 PM
To: 'Darkwah, Mavis'
Subject: RE: Labeling-NDA 204623

Thank you for the email Mavis. I will send a reply before EOB tomorrow. Thanks

From: Darkwah, Mavis [mailto:Mavis.Darkwah@fda.hhs.gov]
Sent: Wednesday, December 11, 2013 2:11 PM
To: Bierman, Bunny

Subject: RE: Labeling-NDA 204623

Importance: High

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Let me know if there are any questions.

Regards,

Mavis

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Importance: High

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Regulatory Health Project Manager

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From: Darkwah, Mavis
Sent: Wednesday, December 11, 2013 3:11 PM
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Subject: RE: Labeling-NDA 204623
Attachments: NDA 204623 draft-pi-07-2013-FDA comments- 11Dec13.doc

Importance: High

Dear Bunny,

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Subject: RE: Labeling-NDA 204623

Dear Bunny,

Attached please find the word version of the labeling, with our response to your proposed changes. Please return a version of the label with our changes accepted and with your proposed changes tracked. Also provide a clean copy of the word version.

We request a response preferably by close of business Friday, November 29, 2013.

Regards,

Mavis

From: Bierman, Bunny [<mailto:Bunny.Bierman@mallinckrodt.com>]
Sent: Thursday, November 14, 2013 2:09 PM
To: Darkwah, Mavis
Subject: RE: Labeling-NDA 204623

Good afternoon Mavis,

Thank you again for sending the labeling changes along. As requested, please find attached a track-changes and clean word version of the label.

If you have any questions, please feel free to contact me.

Is there an ballpark estimate when we could expect to receive the comments on the MG and IFU?

Thanks very much for your time,
Bunny

Bunny Bierman | Regulatory Affairs Manager
Mallinckrodt Pharmaceuticals
675 McDonnell Blvd. | Hazelwood, MO 63042 | USA
T: 314.654.8048
bunny.bierman@mallinckrodt.com | www.mallinckrodt.com

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From: Darkwah, Mavis [<mailto:Mavis.Darkwah@fda.hhs.gov>]
Sent: Tuesday, November 12, 2013 2:25 PM
To: Bierman, Bunny
Subject: Labeling-NDA 204623

Dear Ms. Bierman,

Attached please find the word version of the labeling, with our proposed changes. Please return a version of the label with our changes accepted and with your proposed changes tracked. Also provide a clean copy of the word version. The Med Guide and Instructions for Use with our proposed changes will be sent at a later date.

We request a response preferably by close of business Friday November 15, 2013.

Regards,

Mavis

*Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov*

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19 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Darkwah, Mavis

From: Darkwah, Mavis
Sent: Friday, December 06, 2013 3:19 PM
To: 'Bierman, Bunny'
Subject: RE: Labeling-NDA 204623
Attachments: NDA 204623 MG & IFU FDA comments 06Dec13.doc; NDA 204623 draft-pi-07-2013-FDA comments- 06Dec13.doc

Dear Bunny,

Attached please find the word version of the label, Medication Guide (MG), and Instructions for Use (IFU) with our proposed changes. Please return a version of these labels with our changes accepted and with your proposed changes tracked. Also provide a clean copy of the word version.

We request a response as soon as possible, no later than close of business Tuesday, December 10, 2013.

Let me know if there are any questions.

Regards,

Mavis

From: Bierman, Bunny [<mailto:Bunny.Bierman@mallinckrodt.com>]
Sent: Wednesday, November 27, 2013 8:48 AM
To: Darkwah, Mavis
Subject: RE: Labeling-NDA 204623
Importance: High

Dear Mavis,

Please find attached word version of the label, both clean and changes tracked, with our response to the proposed changes.

Thank you for your time on this and hope you have a nice holiday break.

Bunny

From: Darkwah, Mavis [<mailto:Mavis.Darkwah@fda.hhs.gov>]
Sent: Monday, November 25, 2013 12:31 PM
To: Bierman, Bunny
Subject: RE: Labeling-NDA 204623

Dear Bunny,

Attached please find the word version of the labeling, with our response to your proposed changes. Please return a version of the label with our changes accepted and with your proposed changes tracked. Also provide a clean copy of the word version.

We request a response preferably by close of business Friday, November 29, 2013.

Regards,

Mavis

From: Bierman, Bunny [<mailto:Bunny.Bierman@mallinckrodt.com>]
Sent: Thursday, November 14, 2013 2:09 PM
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Thanks very much for your time,
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Bunny Bierman | Regulatory Affairs Manager
Mallinckrodt Pharmaceuticals
675 McDonnell Blvd. | Hazelwood, MO 63042 | USA
T: 314.654.8048
bunny.bierman@mallinckrodt.com | www.mallinckrodt.com

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To: Bierman, Bunny
Subject: Labeling-NDA 204623

Dear Ms. Bierman,

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We request a response preferably by close of business Friday November 15, 2013.

Regards,

Mavis

*Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager*

*Division of Anesthesia, Analgesia, and Addiction Products
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov*

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Darkwah, Mavis

From: Darkwah, Mavis
Sent: Monday, November 25, 2013 1:30 PM
To: 'Bierman, Bunny'
Subject: RE: Labeling-NDA 204623
Attachments: NDA 204623 draft-pi-07-2013-FDA revised version 25Nov13.doc

Dear Bunny,

Attached please find the word version of the labeling, with our response to your proposed changes. Please return a version of the label with our changes accepted and with your proposed changes tracked. Also provide a clean copy of the word version.

We request a response preferably by close of business Friday, November 29, 2013.

Regards,

Mavis

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Sent: Thursday, November 14, 2013 2:09 PM
To: Darkwah, Mavis
Subject: RE: Labeling-NDA 204623

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Thanks very much for your time,
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T: 314.654.8048
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Sent: Tuesday, November 12, 2013 2:25 PM

To: Bierman, Bunny
Subject: Labeling-NDA 204623

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We request a response preferably by close of business Friday November 15, 2013.

Regards,

Mavis

*Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
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Darkwah, Mavis

From: Darkwah, Mavis
Sent: Tuesday, November 12, 2013 3:25 PM
To: Bierman, Bunny (Bunny.Bierman@mallinckrodt.com)
Subject: Labeling-NDA 204623
Attachments: draft-pi-07-2013-FDA revised version 12Nov13.doc

Dear Ms. Bierman,

Attached please find the word version of the labeling, with our proposed changes. Please return a version of the label with our changes accepted and with your proposed changes tracked. Also provide a clean copy of the word version. The Med Guide and Instructions for Use with our proposed changes will be sent at a later date.

We request a response preferably by close of business Friday November 15, 2013.

Regards,

Mavis

*Mavis Y. Darkwah, Pharm.D.
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
DA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov*

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NDA 204623

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Mallinckrodt Inc.
675 McDonnell Blvd.
Building 30-2
Hazelwood, MO 63042

ATTENTION: Bunny Bierman
Manager, Regulatory Affairs

Dear Ms. Bierman:

Please refer to your New Drug Application (NDA) dated and received May 4, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Diclofenac Sodium Topical Solution, 2%.

We also refer to your correspondence, dated and received August 7, 2013, requesting review of your proposed proprietary name, Pennsaid. We have completed our review of the proposed proprietary name, Pennsaid and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your August 7, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, Lisa Skarupa, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2219. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Mavis Darkwah (240) 402-3158.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
10/07/2013



NDA 204623

MEETING MINUTES

Mallinckrodt Inc.
675 McDonnell Blvd.
Hazelwood, MO 63044

Attention: Bunny Bierman
Manager Regulatory Affairs

Dear Ms. Bierman:

Please refer to your New Drug Application (NDA) dated May 4, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for diclofenac sodium topical solution, 2%.

We also refer to the telecon between representatives of your firm and the FDA on April 25, 2013. The purpose of the meeting was to discuss our complete response letter dated March 4, 2013.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4085.

Sincerely,

{See appended electronic signature page}

Swati Patwardhan
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: End of Review

Meeting Date and Time: April 25, 2013, 12:00 to 1:00 pm
Meeting Location: Teleconference

Application Number: NDA 204623
Product Name: Diclofenac sodium topical solution 2%

Indication: Treatment of the pain of osteoarthritis of the knee(s)
Sponsor/Applicant Name: Mallinckrodt, Inc.

Meeting Chair: Ellen Fields, M.D., MPH
 Clinical Team Leader, Division of Anesthesia, Analgesia, and
 Addiction Products (DAAAP)
Meeting Recorder: Swati Patwardhan, Regulatory Project Manager, DAAAP

FDA	TITLE
Bob A. Rappaport, M.D.	Director, DAAAP
Sharon Hertz, M.D.	Deputy Director, DAAAP
Jacqueline Spaulding, M.D.	Medical Officer, DAAAP
Ellen Fields, M.D., MPH	Clinical Team Leader, DAAAP
Yun Xu, Ph.D.	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology
Jamie Wilkins Parker, PharmD	Team Leader, Division of Medication Error Prevention Analysis (DMEPA)
Vicky Borders-Hemphill, PharmD	Safety Evaluator, DMEPA
Swati Patwardhan, MS	Regulatory Project Manager, DAAAP
Julia Pinto, Ph.D.	Acting Team Lead, Br. VIII, Office of New Drug Quality Assessment (ONDQA)
Mallinckrodt, Inc	TITLE
Mark Mannebach	VP Regulatory Affairs, Mallinckrodt, Inc.
Michael Giuliani	VP R&D, Mallinckrodt, Inc.
Jennifer Weidman,	Director, Regulatory Affairs, Mallinckrodt, Inc.
Bunny Bierman	Manager, Regulatory Affairs, Mallinckrodt, Inc.
Jim Young	VP Clinical Operations, Mallinckrodt, Inc.
Brad Galer	President Pain Group, Nuvo Research Inc.
Michelle Hershoran	Director Regulatory Affairs, Nuvo Research Inc.

BACKGROUND

Mallinckrodt, Inc. submitted an efficacy supplement on May 4, 2012, to support modification of their current 1.5 % formulation to a new 2% formulation with a reduced dosing frequency from four times a day to twice a day for their Pennsaid product (NDA 020947). The Sponsor also submitted a new container closure system (a pump instead of a bottle with a dropper) for the 2% formulation.

As the metered pump was a new container closure, the product was considered a new dosage form, and was therefore accepted as a new NDA (NDA 204623).

NDA 204623 was reviewed for the indication of the treatment (b) (4) of osteoarthritis, and a complete response letter was issued on March 4, 2013. The application was not approved because the reserve samples were not retained at the clinical site for Studies COV05100070 and COV05100175. The March 4, 2013, letter stated that Mallinckrodt must conduct a new relative bioavailability study using their proposed drug diclofenac sodium topical solution, 2% and PENNSAID.

Mallinckrodt submitted a Type A meeting request and meeting package on March 25, 2013, to discuss the March 4, 2013, complete response letter.

DISCUSSION

The questions from the March 25, 2013, meeting package are included below in italic font, the preliminary responses are in bold font, and the discussion is in regular font.

The preliminary comments were sent to Mallinckrodt on April 23, 2013.

After introduction, the discussion focused on Questions 1 and 5.

General

Question 1:

The Complete Response submission will provide data from a new bioavailability study, therefore will be considered a Class 2 resubmission thereby qualifying it for a 6-month PDUFA review period. In the January 16, 2013 teleconference between Mallinckrodt and DAAAP representatives, the Division conveyed they would try to accelerate the review of the PK data during the second review cycle.

Does the Division acknowledge this intention?

FDA Response:

We will try to accelerate review of the PK data during the second review cycle as resources permit. We recommend that you submit your complete response, including the study report for the new bioavailability study, the PK data set, and the bioanalytical

report in a clear and organized manner. A complete and well-organized resubmission will facilitate the review process.

Discussion:

Mallinckrodt inquired if any additional information should be included in the complete response submission along with the new bioavailability study, the PK data set, and the bioanalytical report, as specified in the preliminary response. The Division responded that a complete and detailed description of the PK study and the dataset would aid in reviewing the submission. For example, all abbreviations should be appropriately defined when submitting data sets. Mallinckrodt must also provide an update on any new safety data, including postmarketing data for PENNSAID. If there is no new safety data, then this should be stated in the complete response submission.

Question 2: *Mallinckrodt would like to ensure that the Exclusivity Request provided in Section 1.3.5.3 of the application is sufficiently complete to allow FDA to grant the requested 3-year exclusivity request.*

Does the FDA concur?

FDA Response:

Exclusivity is not determined by the division, but by an exclusivity board. We refer you to the following regulations, 21 CFR 314.50(j);314.108(b)(4) and (5), which describe that a 505 (b)(2) application may be granted three years of Waxman-Hatch exclusivity if one (or more) of the clinical investigations, other than BA/BE studies, is essential to approval of the application and was conducted or sponsored by the applicant.

Discussion:

The preliminary responses were adequate. No further discussion occurred.

Question 3: *Mallinckrodt will be conducting the new bioavailability study at (b) (4) in second quarter of 2013.*

Assuming that the Office of Scientific Investigations (OSI) will need to conduct an inspection of this clinical site, how can Mallinckrodt facilitate the initiation of a timely inspection in order for this process not to become critical path during the second cycle review?

FDA Response:

All parties involved should be prepared for a potential inspection and follow regulatory requirements per 21 CFR 320, including retention of bioavailability reserve samples according to 21 CFR 320.38.

Discussion:

The preliminary responses were adequate. No further discussion occurred

Clinical / Labeling

Question 4: *Mallinckrodt intends to update Section 12.3 of the draft package insert with the diclofenac pharmacokinetic (PK) parameters obtained during the new bioavailability study with PENNSAID 1.5% (NDA 020947) and diclofenac sodium topical solution 2%. Does FDA agree that the draft package insert can be updated to include the PK parameters at the time of the Complete Response submission?*

If yes, Mallinckrodt proposes to provide a revised, marked-up version of the package insert that shows changes, as well as a clean Microsoft Word version.

Does the FDA agree with this proposal?

FDA Response:

We generally agree with your proposal. You may update your proposed label with results from the new relative bioavailability study in the resubmission. The exact content to be included in the final product label will be determined during the review process.

Discussion:

The preliminary responses were adequate. No further discussion occurred.

Proprietary Name

Question 5: *DMEPA advised Mallinckrodt during the NDA review period that the preferred proprietary name for this drug product was “PENNSAID”, the same proprietary name as the approved 1.5% diclofenac sodium topical solution product (NDA 020947).*

Subsequent to those discussions, Mallinckrodt was notified by DAAAP that the indication for the 2% product would be limited to “for the treatment of the pain of osteoarthritis (OA) of the knee(s)”. This indication differs from that of the approved 1.5% product, which is indicated “for the treatment of signs and symptoms of osteoarthritis (OA) of the knee(s)”.

In effort to prevent potential prescriber or medication errors with two diclofenac sodium topical solution products on the market with similar, yet distinct indications with different dosing regimens, Mallinckrodt would like to revisit with DMEPA the use of “2%” to differentiate between the 1.5% and 2% products.

FDA Response:

We continue to not recommend the use of the 2% strength as a component of the proprietary name. Differentiation between products with multiple strengths and dosage forms is best handled via labeling of the product, since modifiers (such as a strength presentation being a component of a proprietary name) may be dropped during prescribing resulting in inadvertent substitution. If the product retains a distinct proprietary name without a modifier and is available as two strengths, it will prompt the prescriber to write a strength on the prescription; and if this is omitted, it will also prompt a pharmacy filling a prescription to inquire about the intended strength to be dispensed, as there will be two distinct products available for selection.

Discussion:

Mallinckrodt agreed not to use the strength as part of the trade name. They asked whether, as the PENNSAID 1.5 % and the proposed 2% diclofenac sodium topical solution will have two different indications, it would be acceptable to use the same trade name for both drug products. The Division responded that the use of trade name 'PENNSAID' is acceptable for both drug products. In response to Mallinckrodt's question regarding a unique trade name for the 2% formulation, the Agency said that any trade name proposal would be reviewed with the NDA resubmission. Mallinckrodt expressed concern that a submission for proprietary name review with the complete response would slow down the review process. The Agency responded that the timeframe for review of a proposed proprietary name during an NDA review cycle is 90 days and, therefore, the best approach is to submit a request for proprietary name review with the NDA resubmission.

Chemistry, Manufacturing and Controls

Question 6: *As the Complete Response Letter was silent on the expiration date of the drug product, Mallinckrodt assumes the requested 24-month tentative expiration dating for the 112g metered-dose bottle is acceptable.*

Does the FDA concur?

FDA Response:

Comments on the recommended expiration dating period for the drug product will be in the final approval letter. Generally, if we do not comment on the expiration dating period during the review, the proposed expiration dating period is granted.

Discussion:

The preliminary responses were adequate. No further discussion occurred

Question 7: *Mallinckrodt would like to update Module 3 in the Complete Response submission to include a*

(b) (4)

All comments received by the Division were accepted.

Does the FDA agree it is acceptable to include this information in the Complete Response Letter?

Does the FDA agree Mallinckrodt has the ability to withdrawal of this information from the Complete Response should this preclude an accelerated second cycle review?

FDA Response:

Since the proposed [REDACTED] (b) (4) is new, adequate stability data (including leachables) are necessary to be able to grant a commercially viable expiry dating period. Your proposal to submit [REDACTED] (b) (4) [REDACTED] does not support a commercially viable expiry period. We recommend that you submit this [REDACTED] (b) (4) in a prior approval supplement as recommended previously.

Discussion:

The preliminary responses were adequate. No further discussion occurred.

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion

ACTION ITEMS

Mallinckrodt should submit a complete and detailed description of the PK study and the dataset with all abbreviations appropriately defined.

Mallinckrodt should provide an update on any new safety data, including postmarketing data for PENNSAID.

ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SWATI A PATWARDHAN
05/20/2013

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Wednesday, February 27, 2013 5:33 PM
To: 'Bierman, Bunny'
Subject: RE: re: Labeling comments for NDA 204623- Feb. 27-2013
Importance: High
Attachments: NDA 204623 draft-pi-FDA revised version-2-27-2013.doc

Dear Ms. Bierman,

Attached please find the word version of the labeling, with our proposed changes. Please return a version of these labels with our changes accepted and with your proposed changes tracked. Also provide a clean copy of the word version.

We request a response preferably by COB Thursday February 28th.

Let me know if there are any questions

Thank you

Swati Patwardhan
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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immediately following this page

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/s/

SWATI A PATWARDHAN
02/28/2013

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Thursday, February 28, 2013 1:53 PM
To: 'Bierman, Bunny'
Subject: RE: Labeling comments for NDA 204623- MG IFU Feb. 28-2013
Importance: High
Attachments: NDA 204623 MG-IFU labeling comments-revised 2-28-2013.doc

Dear Ms. Bierman,

Attached please find the word version of the Med guide and instruction for use , with our proposed changes. Please return a version of these labels with our changes accepted and with your proposed changes tracked. Also provide a clean copy of the word version.

We request a response no later than noon, Friday March 1st. Could please acknowledge the receipt of this email.

Let me know if there are any questions .

Thank you

Swati Patwardhan
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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/s/

SWATI A PATWARDHAN
02/28/2013

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Thursday, February 07, 2013 4:35 PM
To: 'Bierman, Bunny'
Cc: Mannebach, Mark
Subject: RE: Pennsaid 2% (diclofenac 2% solution) NDA-204623
Attachments: Reserve Samples.doc

Dear Ms. Bierman,

1. We contacted OSI regarding your query of the retain samples. Here is their response:

According to Federal Regulation 21 CFR 320.38.:The Clinical site is responsible for retaining the reserve samples, or reserve samples can be stored at an independent third party. In this case samples retained by the Clinical Packaging site do not fulfill the requirements of reserve samples. Agency cannot accept retain samples from clinical packaging site. Attached please find a word document with the description of 21CFR 320.38. for your reference.

2. In addition, we have following request:

We note that you have cross-referenced portions of your previously approved 505(b)(2) application Pennsaid (diclofenac topical solution), NDA 20947, that involved reliance on FDA's finding of safety and/or effectiveness for Voltaren (diclofenac sodium delayed release tablets). Therefore, you should identify Voltaren as relied upon for your pending 505(b)(2) application, NDA 204623, in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement), apply to each listed drug upon which you rely. Please also provide an updated FDA Form 356h that cites reliance on Voltaren.

Thank you

Swati Patwardhan
Phone: 301-796-4085

From: Bierman, Bunny [mailto:Bunny.Bierman@Covidien.com]
Sent: Thursday, February 07, 2013 12:27 PM
To: Patwardhan, Swati
Cc: Mannebach, Mark
Subject: RE: Pennsaid 2% (diclofenac 2% solution) NDA-204623
Importance: High

Dear Swati,

Thank you for the email below. Our Head of Regulatory, Dr. Mark Mannebach, had attempted to contact Dr. Hertz in order to determine if there was any mechanism to obtain the approval by the PDUFA date with post approval commitments. (b) (4)

. Furthermore, Dr. Mannebach feels that if a first cycle approval is not a possibility, then all labeling discussions should be deferred until an approval is possible.

Please contact myself or Dr. Mark Mannebach at (b) (6) for further discussions regarding this application.

Thank you,
Bunny

From: Mannebach, Mark [<mailto:Mark.Mannebach@covidien.com>]
Sent: Tuesday, February 05, 2013 6:14 PM
To: Hertz, Sharon H
Subject: Pennsaid 2% (diclofenac 2% solution) NDA-204623
Importance: High

Dear Dr Hertz,

I want to thank you and the Division for all the feedback and suggestions we received regarding NDA-204623 (diclofenac 2% solution). Unfortunately I was out of the office last week for the last teleconference call. I was hoping you could respond to several follow-up questions that I have for this application.

First, for the draft label, I understand the Division's decision to base the product indication on the results of the pivotal trial COV05100031. Since we only showed statistical significance for Pain Reduction, it is understood why we have a limited indication. (b) (4). My understanding is that you informed us that (b) (4) (i.e., (b) (4) we would have to conduct a 12-week study. My question to you is does it have to be 12-weeks in duration since the original study was 4-weeks? I understand that there would be some risk in not conducting a study with a 12-week duration.

Secondly, the feedback that we would need to repeat the PK studies was disappointing; however, I understand that this is coming from the Scientific Investigations group. (b) (4)

(b) (4)

Lastly, we are in the process of planning the repeat of the PK studies. We are confident we could have the CSRs submitted by this time next year or earlier. I appreciate the willingness expressed in an earlier teleconference call for expediting any future regulatory reviews. Does this still apply?

Again, I would like to thank you and the Division for your guidance and assistance. I look forward to your response and I am willing to discuss in more detail via phone if necessary. I will also be attending the Public Hearing this week in Washington called Impact of Approved Drug Labeling on Chronic Opioid Therapy.

Sincerely,

Mark

Mark Mannebach, RPh, PhD
Vice President Regulatory Affairs
Covidien
Pharmaceutical Sector
675 McDonnell Blvd.
Hazelwood, MO 63042
314-654-6416 (T)
 (b) (6) (C)

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/s/

SWATI A PATWARDHAN
02/07/2013

**PeRC PREA Subcommittee Meeting Minutes
January 30, 2013**

PeRC Members Attending:

Lynne Yao
Hari Cheryl Sachs
Rosemary Addy
Karen Davis-Bruno
Patricia Dinndorf
Tom Smith
Shrikant Pagay
William Rodriguez
Lily Mulugeta
Daiva Shetty
Andrew Mosholder
Colleen LoCicero
Martha Nguyen
Gregory Reaman
Courtney Suggs
Kevin Krudys
Dianne Murphy
Sonal Vaid

Guests Attending:

Melissa Tassinari (PMHS)	Dionna Green (OPT)
Allen Rudman (OCP)	Donna Snyder (PMHS)
Lori Gorski (PMHS)	Amy Taylor (PMHS)
Jeanine Best (PMHS)	Erica Radden (PMHS)
Mitchell Berger (CBER)	Millie Wright (PMHS)
Renan Bonnel (OPT)	Matt Bacho (PMHS)
Michelle Roth-Cline (OPT)	David Lee (OCP)
Jeremiah Momper (OCP)	Vicki Moyer (PMHS)
Ellen Fields (DAAAP)	Dominic Chiapperino (DAAAP)
Cathryn Lee (OND)	Alvina Mushtaq (OCP)
Rupal Shah (OCP)	Ruyi He (DGIEP)
John Trotani (DGIEP)	Stacey Barley (DGIEP)
Anissa Davis (DGIEP)	Jingyu Yu (OCP)
Robert Levin (DPP)	Sonny Sani (DPP)
Nitin Mehrotra (OCP)	

Agenda

[Redacted] (b) (4)

NDA 204623 Pennsaid (b) (4)(diclofenac sodium topical solution) Full Waiver

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

Pennsaid (b) (4) (diclofenac sodium 2% topical solution) Full Waiver

- NDA 204-623, diclofenac sodium 2% topical solution, was studied for the treatment of signs and symptoms of osteoarthritis of the knee.

- The application was submitted on May 4, 2012 and has a PDUFA date of March 4, 2013.
- This application triggers PREA as a new dosage form.
- The Division is requesting a full waiver.
 - Osteoarthritis is on the list of automatic full waivers.
- The PeRC agrees with the full waiver.



NDA 204623

INFORMATION REQUEST

Mallinckrodt, Inc.
Attention: Bunny Bierman
Manager, Regulatory Affairs
Mallinckrodt Inc. (30-2), 675 McDonnell Blvd
Hazelwood, Mo 63042

Dear Ms. Bierman:

Please refer to your New Drug Application (NDA) dated July 13, 2012 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diclofenac 2% topical solution.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a response by **Tuesday, February 5, 2013** in order to continue our evaluation of your NDA.

We have the following comments for your (b) (4)

1.

2.

3.



If you have any questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796 4013.

Sincerely,

{See appended electronic signature page}

Prasad Peri, PhD

Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
01/29/2013

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Friday, January 18, 2013 10:03 AM
To: Bierman, Bunny
Cc: Patwardhan, Swati
Subject: re: NDA 204623 IR- Jan 1-18-2013

Dear Ms. Bierman,
 We are reviewing your pending application NDA 204623 and request a clarification:

In Clinical Study Report COV05100031, on pg. 56 of 106, Table 8 shows the Average Weight of Study Drug Administered Per Dose Calculated from Dispensed and Returned Bottle Weights. Please clarify whether the average weight of study drug administered is mg vs. gm?

Table 8 Average Weight of Study Drug Administered Per Dose Calculated from Dispensed and Returned Bottle Weights

Compliance Assessment	Study Treatment		
	PENNSAID Gel N=130 n (%)	Vehicle Control N=129 n (%)	Total N=259 n (%)
Week 2:			
0 – 1.2 mg	43 (33.1%)	43 (33.3%)	86 (33.2%)
> 1.2 mg - ≤ 1.6 mg	38 (29.2%)	41 (31.8%)	79 (30.5%)
> 1.6 - ≤ 1.8 mg	11 (8.5%)	12 (9.3%)	23 (8.9%)
> 1.8 - ≤ 2.2 mg	22 (16.9%)	22 (17.1%)	44 (17.0%)
> 2.2 - ≤ 2.4 mg	7 (5.4%)	9 (7.0%)	16 (6.2%)
> 2.4 mg	9 (6.9%)	2 (1.6%)	11 (4.2%)
Total non-missing	130 (100%)	129 (100%)	259 (100%)
Week 4:			
0 – 1.2 mg	41 (33.9%)	43 (36.8%)	84 (35.3%)
> 1.2 mg - ≤ 1.6 mg	36 (29.8%)	33 (28.2%)	69 (29.0%)
> 1.6 - ≤ 1.8 mg	9 (7.4%)	10 (8.5%)	19 (8.0%)
> 1.8 - ≤ 2.2 mg	16 (13.2%)	16 (13.7%)	32 (13.4%)
> 2.2 - ≤ 2.4 mg	7 (5.8%)	5 (4.3%)	12 (5.0%)
> 2.4 mg	12 (9.9%)	10 (8.5%)	22 (9.2%)
Total non-missing	121 (93.1%)	117 (90.7%)	238 (91.9%)

Note: The source table displays the average percentage of actual/expected weight of study medication used; from that the average dose weight used can be calculated, which is displayed above in mg/dose for ease of interpretation.

Source: [Table 14.1.12.2.2](#)

Please acknowledge the receipt of this email. We respectfully request a response to this email by COB Tuesday January 23, 2013.

Thank you

Swati Patwardhan
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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/s/

SWATI A PATWARDHAN
01/18/2013

Rivera, Luz E (CDER)

From: Rivera, Luz E (CDER)
Sent: Friday, January 18, 2013 3:10 PM
To: 'Bierman, Bunny'
Subject: NDA 204623 Information Request

Good afternoon Ms. Bierman,

We are reviewing the Chemistry Manufacturing and Control section of your NDA 204623. We need some additional information request from you in order to continue our evaluation.

To aid in review of the supplement, provide the following by **January 24, 2013**:

1. Provide justification for the difference in acceptance criteria for "Description - Contents" for drug product batch release and stability with regards to the color of the solution. Explain what may cause the color change during stability testing and why the color change does not underline a safety and quality concern.
2. Explain why the unknown leachables observed during your accelerated product stability study were not observed in your extractables study. Provide identification information for the "unknown" leachables, if available. Provide validation information for the analytical method used in the leachables study.

Please submit the information via email to me, luz.e.rivera@fda.hhs.gov and officially submit an amendment to the application.

Please acknowledge the receipt of this email.

Please contact me if you have any questions

Thank you,

Luz E Rivera, Psy.D.
LCDR, USPHS
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment III
Phone (301) 796-4013

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/s/

LUZ E RIVERA
01/18/2013



NDA 204623

INFORMATION REQUEST

Mallinckrodt, Inc.
Attention: Bunny Bierman
Manager, Regulatory Affairs
Mallinckrodt Inc. (30-2), 675 McDonnell Blvd
Hazelwood, Mo 63042

Dear Ms. Bierman:

Please refer to your New Drug Application (NDA) dated July 13, 2012 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diclofenac 2% topical solution.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response by Thursday, January 24, 2013 in order to continue our evaluation of your NDA.

1. Provide the following characterization data for your proposed drug product:
 - a) Effect of applied force on the accuracy of dispensing weight per actuation;
 - b) Dispensing weight uniformity from the beginning to the last actuation.

2. Revise the product specification as follows:
 - a) Set the viscosity acceptance criterion of (b) (4) cps for both batch release and stability;
 - b) Tighten the acceptance criterion for (b) (4) to (b) (4) % - (b) (4) %;
 - c) Set the (b) (4) assay acceptance criterion of (b) (4) % (w/w) ((b) (4) % of theoretical content) for both batch release and stability;
 - d) Revise the acceptance criteria for dispensing weight per actuation to be (b) (4) grams (mean) and (b) (4) grams (individual).

3.



If you have any questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796 4013.

Sincerely,

{See appended electronic signature page}

Prasad Peri, PhD
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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PRASAD PERI
01/16/2013



NDA 204623

DISCIPLINE REVIEW LETTER

Mallinckrodt Inc. (30-2)
675 McDonnell Blvd.
Hazelwood, MO 63044

Attention: Bunny Bierman
Manager Regulatory Affairs

Dear Ms. Bierman:

Please refer to your May 4, 2012 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for diclofenac sodium topical solution, metered, 2%.

The Division of Medication Error Prevention and Analysis (DMEPA) has completed their review of the carton and container label and has identified the following deficiencies:

We acknowledge that the proposed proprietary name has not been granted; therefore, we are providing preliminary comments regarding the presentation of the proposed proprietary name on your current labels and labeling.

A. CONTAINER LABEL

1. Revise the proprietary name, active ingredient, and strength statement on the principal display panel so that it appears horizontally oriented (rather than vertical) in order to improve the readability of this important information by standardizing the orientation of the product information. This information should be presented in the same orientation in which the product will typically be stored by patients.
2. Ensure that the established name is ½ the size and prominence of the proprietary name so that it is in accordance with CFR 201.10(g)(2). Additionally, ensure that the proprietary name is presented in the same color and font. Finally, present the double letters “nn” in Pennsaid in regular font. As currently presented it may be confused with the letters “m” or “w”.
3. Increase the prominence of the strength statement “2%” by increasing the font size or some other methods to help further differentiate the proposed Pennsaid product from the currently marketed Pennsaid product, which is 1.5%.

4. Unbold the NDC number and the volume statement so that it is less prominent than other important safety information. Also, relocate the volume statement so that it appears away from the NDC number (e.g. on the bottom part of the principal display panel).
5. Revise the “^{(b) (4)}...” statement to read “Each activation delivers 20 mg of diclofenac sodium.”
6. Remove the “Avoid contact with the eyes or mucous membranes” statement in order to decrease clutter on the principal display panel. If space permits, this statement could be relocated to the back panel.
7. Remove all the instructions from “Apply Pennsaid ^{(b) (4)}” to “After application...” from the back panel to decrease the clutter on the label.
8. Revise the usual dose statement from ^{(b) (4)} “Apply two pump activations to affected knee(s) two times a day.” This format helps highlight that the product may be applied to one or both knees.
9. Remove the color block that surrounds “Mallinckrodt” so that attention is not diverted from important safety information such as name, strength, and Medication Guide statements.

B. CARTON LABELING

1. See comments A2, A3 and A8.
2. Revise the “^{(b) (4)}...” statement to read “each pump activation delivers 20 mg of diclofenac sodium.” Relocate the statement to appear on the side panel where the “rx only” statement currently appears.
3. Remove the “rx only” statement on the side panel because it appears on both the front and the back panel.
4. Relocate the “avoid contact with the eyes or mucous membranes” statement to the side panel so that it appears beneath the instructions for use and decreases clutter on the principal display panel.
5. Relocate the “for external use only” statement so that it appears in the highlighted area of the front and back panel above the “usual dosage:...” statement. Also increase the font size of the usual dosage statement to ensure that the directions for use are highly visible to ensure that patients and practitioners understand that the directions for use for the proposed Pennsaid product are different compared to the currently marketed product.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Swati Patwardhan, Regulatory Project Manager, at (301) 301-796-4085.

Sincerely,

{See appended electronic signature page}

Sara Stradley, MS
Chief Project Management Staff
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SARA E STRADLEY
01/04/2013

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Thursday, October 11, 2012 10:05 AM
To: 'Bierman, Bunny'
Subject: NDA 204623-IR- Oct 11-2012

Dear Ms. Bierman,

We are reviewing your NDA 204623 and request additional information as follows:

We refer to Table 8 (i.e., Average Weight of Study Drug Administered per Dose Calculated from Dispensed and Returned Bottle Weights) located in Clinical Study Report COV05100031. In this table we note the wide variability of dosing at Weeks 2 and 4. Given Week 2 data, were there any attempts to correct the wide variability of dosing noted among subjects in both treatment groups?

Please acknowledge the receipt of the email and provide a timeline for response

Thank you

Swati Patwardhan
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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/s/

SWATI A PATWARDHAN
10/11/2012

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Wednesday, October 03, 2012 3:35 PM
To: 'Bierman, Bunny'
Subject: RE: NDA 204623 Information request Oct-3-2012

Dear Ms. Bierman,

We are reviewing your pending application, NDA 204623, and request following information:

As we requested in 74-day letter dated July 17, 2012, we asked you to provide individual and summary data for AUC0-6 and AUC0-12 on Day 8 for subjects administered 2% Pennsaid topical solution, 1.5% PENNSAID topical solution and oral diclofenac tablets in Study COV05100070 and COV05100175. In your response dated 8/22/12, you only provided the summary data (mean, median, etc) for AUC0-6 and AUC0-12 for the individual studies and summary data tables for these studies.

- Provide individual subject data for AUC0-6 and AUC0-12 on Day 8 for Study COV05100070 and COV05100175, and
- conduct BE analysis for AUC0-6 and AUC0-12.

Please acknowledge receipt of this email and submit a response to the NDA by COB October 26, 2012. In addition, a copy of your response submitted by e-mail (swati.patwardhan@fda.hhs.gov) will expedite review of your request. In your cover letter refer to the date on which this information was requested.

Thank you

Swati Patwardhan
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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/s/

SWATI A PATWARDHAN
10/03/2012



NDA 204623

INFORMATION REQUEST

Mallinckrodt, Inc.
Attention: Bunny Bierman
Manager, Regulatory Affairs
675 McDonnell Blvd
Hazelwood, Mo 63042

Dear Ms. Bierman:

Please refer to your New Drug Application (NDA) dated July 13, 2012 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diclofenac 2% topical solution.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

There are three pivotal clinical/PK studies for this NDA to support the new formulation and container/closure. For two of those studies, you indicated the use of a bottle/pump system that differs from the proposed commercial system.

- Provide a comparison of the batch analysis data upon release and stability for the drug product supplies used in the clinical studies COV05100031, COV05100175, and COV05100070. Include assay, impurities/degradants and delivered dose (dispensed weight per actuation).

If you have any questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796 4013.

Sincerely,

{See appended electronic signature page}

Prasad Peri, PhD
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
09/06/2012



NDA 204623

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Mallinckrodt, Inc. (30-2)
675 McDonnell Blvd.
Hazelwood, MO 63044

ATTENTION: Bunny Bierman
Manager, Regulatory Affairs

Dear Ms. Bierman:

Please refer to your New Drug Application (NDA) dated and received May 4, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Diclofenac Sodium Topical Solution, 2% w/w.

We also reference our teleconference held July 26, 2012, providing preliminary comments to you on the proposed proprietary name, [REDACTED] (b) (4).

We acknowledge receipt of your correspondence dated and received July 31, 2012, notifying us that you are withdrawing your request for a review of the proposed proprietary name [REDACTED] (b) (4). This proposed proprietary name request is considered withdrawn as of July 31, 2012.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, a new request for a proposed proprietary name review should be submitted. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Danyal Chaudhry, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Swati Patwardhan at (301) 796-4085.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

AZEEM D CHAUDHRY
08/03/2012

CAROL A HOLQUIST
08/03/2012

*****For Internal Use Only*****

Proposed Trade Name: (b) (4)

NDA 204623

Sponsor: Mallinckrodt, pharmaceuticals business of Covidien

Sponsor Teleconference July 26, 2012, 12:00 PM Location: WO. 22, Rm 5157

Purpose of FDA Requested Teleconference:

To discuss the safety issues regarding the proposed trade name (b) (4) submitted under NDA 204623

Discussion & Agreements:

FDA stated that while it is agreed upon that the modifier “(b) (4)” communicates that the (b) (4), the modifier does not convey the change in formulation (from 1.5% to 2%) or the change in dose or frequency of administration. Furthermore, post marketing surveillance of medication errors demonstrates that modifiers can be dropped or omitted during the drug use process. This type of error was also identified during FDA prescription simulation studies in which respondents interpreted the name as “Pennsaid”, rather than, “(b) (4)”. Therefore, we recommend marketing the proposed product under the name Pennsaid and highlighting the differences (i.e. strength) in the labels and labeling.

FDA recommended the Applicant can choose to withdraw the proposed trade name (b) (4) and resubmit the new name for our evaluation.

Mallinckrodt inquired if they had the option to submit a different name other than Pennsaid. FDA stated that Mallinckrodt is free to submit Pennsaid or a different alternate name for review but FDA cannot comment on the acceptability of the alternate name and it would be a review issue. The Applicant agreed to consider Agency’s advice and to provide feedback regarding subsequent steps for their trade name review (withdrawal and re-submission) by Monday, July 30, 2012.

Meeting Participants:

FDA:

Lubna Merchant, PharmD, M.S.: Team Leader, Division of Medication Errors and Prevention Analysis, Office of Surveillance & Epidemiology

Anne Tobenkin, PharmD: Safety Evaluator, Division of Medication Errors and Prevention Analysis, Office of Surveillance & Epidemiology

Danyal Chaudhry: Safety Regulatory Health Project Manager, Office of Surveillance & Epidemiology

Mallinckrodt:

Bunny Bierman, Manager Regulatory Affairs

Jennifer Lierman, Director of Marketing

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/s/

AZEEM D CHAUDHRY
07/26/2012
DMEPA Teleconference



NDA 204623

FILING COMMUNICATION

Mallinckrodt Inc. (30-2)
675 McDonnell Blvd.
Hazelwood, MO 63044

Attention: Bunny Bierman
Manager Regulatory Affairs

Dear Ms. Bierman:

Please refer to your New Drug Application (NDA) dated and received May 4, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Pennsaid (diclofenac sodium) topical solution, metered, 2%.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is March 4, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by February 4, 2013.

We request that you submit the following information:

1. After preliminary review of studies COV05100170 and COV05100175, it appears both 2% PENNSAID and 1.5% PENNSAID were not dosed the entire 24 hours on Day 8. Provide individual and summary data for AUC₀₋₆ and AUC₀₋₁₂ on Day 8 for subjects administered 2% PENNSAID topical solution, 1.5% PENNSAID topical solution, and oral diclofenac tablets in these studies.
2. The final to-be-marketed container-closure system was not used in the Phase 2 clinical

efficacy and safety study COV05100031, and relative BA study COV05100170. Clarify if the delivery performance is the same between the two systems. Provide details of the differences between the two container-closure systems.

3. Provide bridging data between the two container-closure systems as appropriate.
4. You submitted tabulation datasets for study COV05100031. However, we cannot locate your analysis datasets for this study. Provide the location of the analysis datasets in the submission. If the datasets were not included, submit the analysis datasets with the define documents and SAS programs used for the summary tables in the clinical study report.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. The length of the HIGHLIGHTS (HL) section must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement).
2. White space must be present before each major heading in the HL.
3. Each summarized statement in the HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g., end of each bullet).
4. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI without numbering as a subsection upon approval.
5. You must reference FDA-approved patient labeling. Use the following statement at the beginning of Section 17:

See FDA-approved patient labeling (Medication Guide and Instructions for Use)

We request that you resubmit labeling that addresses these issues by August 7, 2012. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form

with annotated references, and the proposed package insert (PI), Medication Guide, and Instruction for Use (IFU). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and Instruction for Use, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Swati Patwardhan, Regulatory Project Manager, at (301) 796-4085.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BOB A RAPPAPORT
07/17/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 16, 2012

TO: File

**THROUGH: Sara Stradley, Chief Project Management Staff, Division of Anesthesia,
Analgesia, and Addiction Products**

FROM: Swati Patwardhan

SUBJECT: Receipt of new application NDA 204623

APPLICATION/DRUG: NDA 204623

Mallinckrodt, Inc. submitted an efficacy supplement on May 4, 2012, under NDA 20947, to modify their current 1.5 % formulation to a new 2% formulation with a reduced dosing frequency from 4 times a day to twice a day. This supplement was identified as S009.

The Sponsor also submitted a new container closure system, a pump instead of a bottle with a dropper that will be used to market the 2 % formulation. From discussion with the User Fee staff during the filing review period, it was determined that the new container closure system is intended to ensure delivery of a consistent amount of drug per actuation making it a new dosage form - a metered pump. Therefore, this is a new NDA and not an efficacy supplement. The Orange Book staff and Office of General Counsel concurred with this evaluation (via email, see attached).

On June 28, 2012, a teleconference was held the applicant to notify them about this development. Mallinckrodt was requested to resubmit the May 4, 2012, supplemental submission (S-009) under the new NDA number - 204623. Mallinckrodt was assured that the review cycle and the PDUFA goal date would not be affected by this resubmission. **The submission date and receipt date of the NDA 204623 will be considered as May 4, 2012 (the day when the submission was submitted under NDA 20947 as S-009)**, as per the attached July 5, 2012, email from Virginia Hussong of the eData Management Solutions Team.

The filing reviews finalized in DARRTS under S009 will be moved over to the new NDA 204623.

Concurrence by:

M. Sullivan 7/13/2012

S. Stradley 7/16/2012

Attachments:

APPEARS THIS WAY ON ORIGINAL

Patwardhan, Swati

From: Jones, Michael D
Sent: Thursday, June 28, 2012 10:38 AM
To: Read, David T; Shimer, Martin
Cc: Patwardhan, Swati; Stradley, Sara; Sullivan, Matthew; Tierney, Julia; Berlin, Robert; Friedman, Beverly J; Jones, Ashley R; Hertz, Sharon H
Subject: RE: Higher dose formulation for topical - Pennsaid

Thanks Guys.

Swati/Sharon - see below.

We're good to go.

Mike

From: Read, David T
Sent: Thursday, June 28, 2012 10:31 AM
To: Shimer, Martin
Cc: Jones, Michael D
Subject: RE: Higher dose formulation for topical - Pennsaid

Thanks, Marty.

Mike, I think we're on board here. The Pennsaid products are pretty clearly labeled for a specific dose, e.g., Solution - 40 drops per knee.

From: Shimer, Martin
Sent: Thursday, June 28, 2012 10:21 AM
To: Read, David T
Cc: Jones, Michael D
Subject: RE: Higher dose formulation for topical - Pennsaid

Dave-my take on when we need to indicated that a product is a 'metered pump' dosage form hinges entirely on what function the metered pump performs. If the metered pump is designed to deliver a specific dose of the product as indicated by the labeling, then the product should be designated as a metered pump solution, gel, cream etc. etc. If the metered pump is simply for convenience and the labeling merely indicates that one or two pumps of the product are to be applied to the affected area or the product itself doesn't have specific dosing considerations then it should not be entered into the OB as a metered pump. Examples of this later situation would be acne preparations that are applied "as a thin film" to the affected area. I believe(but could be wrong since I'm trying to rely upon memory of my behind the counter pharmacy days more than 10 years ago) that some of the Differin products were available in what I would characterize as a convenience pump-thus not a true metered pump. I think the other consideration for us is whether we are going to have to require generics to design a similar pump. Since it appears that the proposed innovator product is going to be available in a pump that will reproducibly deliver 1 mL per actuation, then the generics are going to have to follow suit. This also points to the Agency listing the NDA product as a metered pump. If we were to list the product in the OB as just simply a solution then potential ANDA applicants could suggest that it isn't imperative that their product use a metered pump.

Tx,

Marty

From: Read, David T

Sent: Thursday, June 28, 2012 9:43 AM
To: Shimer, Martin
Cc: Jones, Michael D
Subject: RE: Higher dose formulation for topical - Pennsaid

Marty - What's your quick take on this? Different dosage form?

From: Read, David T
Sent: Thursday, June 28, 2012 9:21 AM
To: Jones, Michael D
Subject: RE: Higher dose formulation for topical - Pennsaid

Mike-

Just talked to Harvey. Before making a decision on this, he'd really like to wait until Mary Ann returns on Monday. I don't think we can get a firm decision to you before the 11 am meeting. Does the "needs a new NDA" decision totally hinge on this, or does the fact that they are not q and q lead to the same conclusion?

Dave

From: Jones, Michael D
Sent: Thursday, June 28, 2012 8:36 AM
To: Read, David T
Subject: RE: Higher dose formulation for topical - Pennsaid

Thanks Dave.

m

From: Read, David T
Sent: Thursday, June 28, 2012 8:21 AM
To: Jones, Michael D
Cc: Holovac, Mary Ann; Greenberg, Harvey A; Reinwald, Robert L
Subject: RE: Higher dose formulation for topical - Pennsaid

Harvey, Mary Ann, and Bob-

Can one of you give me a call about this? Mike is pestering me for an OB decision on the metered pump dosage form question. I'm inclined to agree that this case - in which the AI is absorbed via DMSO - is closer to the testosterone gel model than it is to true topical product.

Dave

From: Jones, Michael D
Sent: Monday, June 25, 2012 12:45 PM
To: Hertz, Sharon H
Cc: Friedman, Beverly J; Jones, Ashley R; Duffy, Eric P; Lippmann, Elaine; Tierney, Julia; Read, David T; Holovac, Mary Ann; Greenberg, Harvey A; Reinwald, Robert L; Shimer, Martin; Berlin, Robert; Ripper, Leah W; Jani, Parinda
Subject: RE: Higher dose formulation for topical - Pennsaid

Folks

I just attended a RTF meeting for this submission and they were asking the status on the dosage form decision.

Sharon has a few clarifications.

Mike

From: Jones, Michael D
Sent: Tuesday, June 19, 2012 2:19 PM
To: Ripper, Leah W
Cc: Friedman, Beverly J; Jones, Ashley R; Duffy, Eric P; Lippmann, Elaine; Tierney, Julia; Read, David T; Holovac, Mary Ann; Greenberg, Harvey A; Reinwald, Robert L; Shimer, Martin; Berlin, Robert
Subject: RE: Higher dose formulation for topical

Lee

Looks like this supplement is more than just going from 1.5% to 2%.

It also looks like this is a product for systemic use that it is going from a topical solution that is dosed at 40 drops (the bottle has a dropper cap, able to dispense in drops) per knee 4 times a day to a topical metered solution (i.e., the new product is a metered pump) that is dosed at 2 mLs (i.e., 2 pumps) per knee twice a day. I've included the revised package insert labeling.

According to our bundling policy if the product has the same active ingredient, same route of administration, and same dosage form (for the same dosage form you need to be q and q identical), then you can be a supplement. There is one more item to the bundling policy. It also says that if you have differences in excipients that require separate clinical studies of safety or effectiveness, because of the differences in excipients then you should submit a separate application.

What it looks like here is that you have the same active ingredient (i.e., diclofenic sodium), the same route of administration (i.e., topical), but you have a different dosage form (the orange book shows we have solutions and solutions, metered) and the two solutions are not q and q identical. I'm assuming the clinical data required for approval is not because of the inactive ingredients, but rather because of the new dosing, etc. The division should confirm this assumption.

All that said it looks like we should have expected a new NDA rather than a supplement.

Does anybody have any contrasting opinions as to whether this is a new dosage form?

Mike

<< File: annotated-draft-labeling-text.pdf >>

From: Ripper, Leah W
Sent: Tuesday, June 19, 2012 1:42 PM
To: Jones, Michael D

Cc: Friedman, Beverly J; Jones, Ashley R
Subject: RE: Higher dose formulation for topical

Supplement 9, currently logged in as an efficacy supplement

From: Jones, Michael D
Sent: Tuesday, June 19, 2012 8:00 AM
To: Ripper, Leah W
Cc: Friedman, Beverly J; Jones, Ashley R
Subject: RE: Higher dose formulation for topical

Potentially it can be a supplement. But need more details.
What's the supplement number?

M

From: Ripper, Leah W
Sent: Monday, June 18, 2012 5:30 PM
To: Jones, Michael D
Subject: Higher dose formulation for topical

Mike, we have approved NDA 20947 for 1.5% diclofenac topical solution. Applicant has submitted a supplement for 2% topical solution. I'm emailing just to confirm that this can be a supplement, doesn't have to be a new NDA.

Lee

Lee W. Ripper
Associate Director for Regulatory Affairs
Office of Drug Evaluation II, OND, CDER, FDA
Silver Spring, MD 20903
Phone: 301-796-1282 / Fax: 301-796-9717
Email: Leah.Ripper@fda.hhs.gov

Patwardhan, Swati

From: Hussong, Virginia
Sent: Thursday, July 05, 2012 3:25 PM
To: Jones, Michael D; Patwardhan, Swati; Gensinger, Gary M
Cc: Friedman, Beverly J; Jones, Ashley R; Sullivan, Matthew; Stradley, Sara; Jani, Parinda; Stone, L. Gail; Gensinger, Gary M; Shkiler, Marina; Hamann, Hilmar; Gray, Mark (CDER)
Subject: RE: NDA 20947/S-009 decision to file

Hi -

Here is the process we came up with:

1. New NDA numbers must be obtained for existing NDAs 020947 (s-009) and 204200. The PMs assigned for each application should request this from cderrappnumrequest@fda.hhs.gov and relay this information to the sponsor.
2. Sponsors should be instructed submit to the new NDAs. They can either re-submit all the appropriate files for review (recommended), or if the division agrees, the sponsor can submit a cover letter in addition to a cross-reference to the existing NDAs, where the files can be found. The division should make this call, and the respective PMs should communicate these instructions to the sponsors. The sponsor can be referred to ESUB@fda.hhs.gov for any additional assistance needed regarding eCTD.
3. The DARRTS dates for the new NDAs will need to match the existing NDA dates. For each NDA, a memo should be prepared and checked into DARRTS that clearly explains why the new NDA is being created, and the fact that the dates were manually changed in order to match the existing NDAs.

There is an internal question about #3 that needs to be resolved, but in the meantime I think the division should move ahead with #1. Let me know if you want a t-con to discuss.

Thanks,

Ginny Hussong

eData Management Solutions Team, CDER
U.S. Food and Drug Administration
Phone: (301) 796-1016
Virginia.Hussong@fda.hhs.gov

From: Jones, Michael D
Sent: Thursday, July 05, 2012 3:03 PM
To: Patwardhan, Swati; Gensinger, Gary M
Cc: Friedman, Beverly J; Jones, Ashley R; Sullivan, Matthew; Stradley, Sara; Jani, Parinda; Stone, L. Gail; Gensinger, Gary M; Hussong, Virginia; Shkiler, Marina; Hamann, Hilmar
Subject: RE: NDA 20947/S-009 decision to file

[Gary/Ginny/Gail](#)

[See below.](#)

[Next step?](#)

M

From: Patwardhan, Swati
Sent: Thursday, July 05, 2012 2:59 PM
To: Jones, Michael D; Gensinger, Gary M
Cc: Friedman, Beverly J; Jones, Ashley R; Sullivan, Matthew; Stradley, Sara; Jani, Parinda
Subject: RE: NDA 20947/S-009 decision to file

Hi Gary/Mike,
Can you please let us know when we will receive a new NDA number.

Swati Patwardhan
Phone: 301-796-4085

From: Patwardhan, Swati
Sent: Tuesday, July 03, 2012 11:13 AM
To: Jones, Michael D; Gensinger, Gary M
Cc: Friedman, Beverly J; Jones, Ashley R; Sullivan, Matthew; Stradley, Sara; Jani, Parinda
Subject: RE: NDA 20947/S-009 decision to file

Hi Mike/Gary,
Can you provide any update on when we will receive the NDA number, and what are the next steps

Swati Patwardhan
Phone: 301-796-4085

From: Jones, Michael D
Sent: Monday, July 02, 2012 3:36 PM
To: Patwardhan, Swati; Gensinger, Gary M
Cc: Friedman, Beverly J; Jones, Ashley R; Sullivan, Matthew; Stradley, Sara; Jani, Parinda
Subject: RE: NDA 20947/S-009 decision to file

Thanks Swati.

m

From: Patwardhan, Swati
Sent: Monday, July 02, 2012 3:31 PM
To: Jones, Michael D; Gensinger, Gary M
Cc: Friedman, Beverly J; Jones, Ashley R; Sullivan, Matthew; Stradley, Sara; Jani, Parinda
Subject: RE: NDA 20947/S-009 decision to file

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SWATI A PATWARDHAN
07/16/2012

MATTHEW W SULLIVAN
07/16/2012

SARA E STRADLEY
07/16/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

PIND 75,045

Nuvo Research, Inc.
7560 Airport Road, Unit 10
Mississauga, ON
Canada L4T 4H4

Attention: Mimi Diva Brennan, BScM.T., A.R.T., C.I.M
Director, Clinical Research and Regulatory Affairs

Dear Ms. Brennan:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Pennsaid Gel (diclofenac sodium) topical gel, 2% w/w.

We also refer to the meeting between representatives of your firm and the FDA on August 28, 2008. The purpose of the meeting was to obtain Agency guidance regarding your proposed drug development program.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

Tanya Clayton
Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 28, 2008

TIME: 12:00-1:00 pm

LOCATION: White Oak, Building 22, Conference Room 1315

APPLICATION: Pre-IND

DRUG NAME: PENNSAID® Gel (diclofenac sodium topical gel) 2% w/w

INDICATION: Topical solution to relieve the pain [REDACTED] ^{(b) (4)} of osteoarthritis of the knee, with twice a day dosing

TYPE OF MEETING: Type B, Pre-IND

MEETING CHAIR: Sharon Hertz, M.D., Deputy Division Director

MEETING RECORDER: Tanya Clayton, Regulatory Project Manager

FDA Attendees	Title
Curtis Rosebraugh, M.D.	Director, ODE II
Sharon Hertz, M.D.	Deputy Division Director
Robert Shibuya, M.D.	Clinical Team Leader
Neville Gibbs, M.D.	Clinical Reviewer
Adam Wasserman, Ph.D.	Supervisory Pharmacologist
Lawrence Leshin, Ph.D.	Pharmacology/Toxicology Reviewer
Thomas Permutt, Ph.D.	Director, Office of Biostatistics
Dionne Price, Ph.D.	BioStatistics Team Leader
Joan Buenconsejo, Ph.D.	BioStatistics Reviewer
Tanya Clayton	Regulatory Health Project Manager
(Nuvo Research)Attendees	Title
Daniel Chicoine	Chairman
Bradley Galer, M.D.	Vice President, Pain Products
John London	Vice Chairman
Mimi Brennan, BScM.T., A.R.T., C.I.M	Director, Regulatory Affairs & Clinical Research
Michelle Hershoran, B.Sc.	Manager, Global Regulatory Affairs
[REDACTED] ^{(b) (4)}	Consultant

Linked Applications

Sponsor Name

Drug Name

IND 75045

NUVO RESEARCH,INC

DICLOFENAC SODIUM TOPICAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TANYA D CLAYTON

10/01/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 75,045

Dimethaid International Inc.
Los Abedules, Appleby Gardens
St. James, Barbados

Dimethaid International Inc. is fully-owned subsidiary of Nuvo Research Inc.
7560 Airport Road, Unit #10
Mississauga, ON, CANADA, L4T 4H4

Attention: Mimi Brennan
Director, Regulatory Affairs & Clinical Research

Dear Ms. Brennan:

Please refer to your Pre-Investigational New Drug Application (PIND) file for PENNSAID® Gel (2% diclofenac sodium) topical NSAID formulation with a twice a day (b.i.d.) dosing regimen.

We also refer to the meeting between representatives of your firm and the FDA on September 25, 2006. The purpose of the meeting was to discuss the PENNSAID® Gel (2% diclofenac sodium) drug development program as a product line extension of PENNSAID® topical solution (1.5% w/w diclofenac sodium solution).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Lauren Tornetta, Regulatory Project Manager, at (301) 796-2246.

Sincerely,

{See appended electronic signature page}

Lauren Tornetta, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 25, 2006

TIME: 12:30 p.m. – 1:30 p.m.

LOCATION: Bldg.22, White Oak Conference Room 1309

APPLICATION: PIND 75,045

DRUG NAME: PENNSAID® (2% diclofenac sodium) topical NSAID

TYPE OF MEETING: Type B/ End-of-Phase 2

MEETING CHAIR: Rigoberto Roca, M.D., Deputy Division Director

MEETING RECORDER: Lauren Tornetta, M.S., Regulatory Project Manager

FDA ATTENDEES: Bob Meyer, M.D., Director, Office of Drug Evaluation II (ODE II)
Curtis Rosebraugh, M.D., Deputy Director, ODE II
Bob Rappaport, M.D., Division Director
Rigoberto Roca, M.D., Deputy Division Director
Ali Al Hakim, Ph.D., Pharmaceutical Assessment Lead
Jeff Siegel, M.D., Medical Team Leader
Sarah Okada, M.D., Medical Officer
Sarah Cochran, M.D., Medical Officer
David Lee, Ph.D., Clinical Pharmacology Reviewer
Dan Mellon, Ph.D., Pharmacology/Toxicology Team Leader
Elizabeth Bolan, Ph.D., Pharmacology/Toxicology Reviewer
Dionne Price, Ph.D., Statistical Team Leader
Yongman Kim, Ph.D., Statistical Reviewer
Janice Weiner, J.D., M.P.H., Regulatory Counsel, ORP
Lauren Tornetta, M.S., Regulatory Project Manager
Lisa Malandro, Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Henrich Guntermann, M.D., M.Sc., President / CEO
Daniel Chicoine, Chairman
John London, Vice Chairman
Jagat Singh Ph.D., Director Research and Development
Zev Shainhouse, M.D., Medical Director
Maria Burian, M.D., Ph.D., Medical Project Leader
Mimi D. Brennan, Director Regulatory Affairs & Clinical Research
Michelle Hershoran, B.Sc., Manager Global Regulatory Affairs
(b) (4), Consultant
(b) (4), Consultant

BACKGROUND:

The purpose of this meeting is to discuss the PENNSAID® Gel (2% diclofenac sodium) drug development program as a product line extension of PENNSAID® Topical Solution (1.5% w/w diclofenac sodium solution) (see NDA 20-947 and IND 42,773).

The basis for submission of PENNSAID® Gel (2% diclofenac sodium) is a 505(b)(2) NDA with reference to PENNSAID® Topical Solution (1.5% w/w diclofenac sodium) (NDA 20-947) and Voltaren Tablets. Dimethaid is developing PENNSAID® Gel (2% diclofenac sodium) with a twice a day dosing regiment in order to improve patient compliance and to further treatment options for the physician.

MEETING OBJECTIVES:

The meeting objectives for this End-of-Phase 2 meeting are as follows:

1. Obtain guidance from the Division in conducting the proposed overall drug product development plan for PENNSAID® Gel (2% diclofenac sodium).
2. Obtain agreement from the Division for the design of [REDACTED] (b) (4) [REDACTED] as the primary basis for approval of a 505(b)(2) NDA.

ACTION ITEMS:

1. The Sponsor will submit a rationale/justification to support the appropriateness of their post-hoc analysis for the 2.0% Gel formulation of PENNSAID® to be reviewed by the Division (Question 1).
2. The Division will clarify and confirm its position on the need to include multiple reference listed drugs (RLDs) in the Sponsor's Pharmacokinetic (PK) study design (Question 4).
3. The Division will clarify its position on evaluating the adequacy and generalizability of the topical safety studies of the 1.5% diclofenac formulation for supporting the use of the 2% diclofenac gel formulation (Question 5).
4. The Division will clarify its position on submitting a special protocol assessment (SPA) to a PIND.

DISCUSSION POINTS:

The Sponsor's questions are presented below in *italicized text*. Agency responses, prepared and forwarded to the Sponsor prior to the meeting, are **bolded**. Following introductions, the discussion was focused on Questions 1, 2, 4, 5, 6 and 7. Discussion related to these questions is presented in normal text.

OVERALL DEVELOPMENT PLAN

Question 1: Is the proposed PENNSAID® Gel (2% diclofenac sodium) development plan, as provided in Section 9 (Clinical Data Summary), Section 10 (Preclinical Data Summary) and Section 11 (CMC Data Summary), acceptable for obtaining approval as a 505(b)(2) NDA?

FDA Response:

Clinical:

You are proposing to submit one efficacy study with PENNSAID Gel, along with clinical and pre-clinical data from the PENNSAID 1.5% topical solution studies and the published literature in order to seek approval for PENNSAID 2% Gel as a 505(b)(2) application.

Assuming the PENNSAID 1.5% topic solution is approved and your efficacy study of PENNSAID 2% gel is positive then in principle this proposed package would be acceptable for submission of an NDA. Whether the data you are proposing will be sufficient to support NDA approval can only be determined upon review of the data.

For approval, you will need to provide evidence that PENNSAID 2% Gel is safe and effective. If you intend to rely on evidence from clinical trials of the PENNSAID 1.5% topical solution to support your proposed single clinical trial for PENNSAID 2% Gel you will also need to provide evidence that these two products are sufficiently similar, for example, with comparative bridging PK data.

Nonclinical:

No. Studies to characterize the potential for dermal carcinogenicity and dermal photocarcinogenicity for this topical product are missing from your nonclinical development program.

It is not clear from your meeting package what you mean by your proposal to rely on “...other information on file with the Agency” to support the nonclinical safety of the active ingredient diclofenac sodium.

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency’s regulations at 21 CFR 314.54 and the October 1999 Draft Guidance for Industry “Applications Covered by Section 505(b)(2)” available at <http://www.fda.gov/cder/guidance/guidance.htm> for further information.

DISCUSSION:

For their 505(b)(2) NDA, the Sponsor clarified that they intend to primarily rely upon the Agency’s finding of safety and effectiveness for Voltaren® (oral diclofenac) and may also rely upon the Agency’s finding of safety for Solaraze® Gel (a 3% diclofenac topical formulation) if they are unable to obtain a right of reference to Solaraze® nonclinical data. They also intend to

use the nonclinical and clinical data from their studies of the PENNSAID® 1.5% solution to support this NDA. (PENNSAID® 1.5% solution is currently unapproved and, therefore, there is no FDA finding of safety or effectiveness upon which the Sponsor may rely.) Further discussion centered around the additional studies and measures that would be required.

The Sponsor stated that they are planning to perform a bridging PK study comparing the 1.5% Solution vs. 2.0% Gel formulation of PENNSAID®. The Division confirmed that this would be required if the Sponsor intends to use data from the 1.5% PENNSAID® nonclinical and clinical studies to support their NDA for the 2% PENNSAID® gel. However, as noted in the response to question 4, for a 505(b)(2) application, comparative PK studies should also be performed using the listed drug(s) relied upon. Although the you proposed to rely upon the Agency's finding of safety and effectiveness for Voltaren®, you also intend to use data for Solaraze® gel for the dermal carcinogenicity and dermal photocarcinogenicity studies. (See discussion of question 4 regarding the necessity of a bridging PK study using Solaraze®.) The Sponsor stated that they are actively attempting to obtain right of reference for these dermal carcinogenicity studies to submit with the PENNSAID® 2% Gel NDA. However, if they are unable to acquire rights to these data, the Sponsor asked whether they could rely upon the Agency's previous finding of safety for Solaraze®, and perform the carcinogenicity studies as a Phase 4 commitment. The Division responded that required safety studies would most likely not be allowed to be delayed until Phase 4. Furthermore, the Division noted, as a caveat, that filing or approval of a 505(b)(2) application may be delayed due to patent or exclusivity protections covering the listed drug(s) upon which the Sponsor chooses to rely. While this is not an issue with Voltaren®, it may be an issue with Solaraze®.

Post-Meeting Note:

As PENNSAID® 1.5% solution is the subject of a pending NDA, there is no FDA *finding* of safety or effectiveness for the sponsor to rely upon in support of a 505(b)(2) application. However, you may reference its own studies (i.e., studies conducted by or for the Sponsor) to support its clinical development program for PENNSAID® 2% gel while the NDA for PENNSAID® 1.5% solution is pending. The adequacy of such studies to support approval is a review issue.

CMC QUESTION

Question 2: The proposed clinical batch stability protocol for PENNSAID® Gel (Protocol No. RD-011, rev.00) is provided for review (see Appendix 12.7 of the Briefing Package), as this batch will be considered as one of the three required batches for the pre-marketing stability program. Does the Division agree?

FDA Response:

- 1. Include a homogeneity test in the drug product release and stability specifications (test for the top, middle and bottom of the bottle).**
- 2. Include “absence of phase separation” in the description test for the drug product**
- 3. Due to the high amount of DMSO present in the drug product, it is recommended that you perform leachables and extractables test between the drug product gel and the container/closure system**

Additional CMC comments

1. Provide description and performance of the delivery system (e.g. delivery of (b) (4) mL form the (b) (4) mL bottle) considering the multi-dose nature of the delivery system
2. Include identification/specifications tests for the incoming diclofenac sodium drug substance material
3. Provide a well documented pharmaceutical development report as per ICH-Q8
4. Provide CFN numbers, names and addresses of all sites involved in manufacturing, testing, stability, packaging of the drug product
5. Provide adequate amount of stability data to cover the proposed expiry dating of the drug product

DISCUSSION:

In reference to Point #2 under “Additional CMC comments,” the Sponsor stated that it would be

(b) (4)

. Dr. Al Hakim suggested that,

(b) (4)

PRECLINICAL QUESTIONS

Question 3: No additional preclinical toxicology studies are planned with the final to-be-marketed formulation. Does the Division agree?

FDA Response:

As noted in the response to Question 1, studies to characterize the potential for dermal carcinogenicity and dermal photocarcinogenicity for this topical product are missing from your nonclinical development program.

If you are considering submission of a 505(b)(2) application, then you may be able to rely on studies not conducted by or for you and to which you have not obtained a right of reference or use (i.e., published literature or the Agency’s finding of safety and/or effectiveness for a listed drug) to support your nonclinical development program in these areas.

DISCUSSION: See discussion section for questions 1 and 4.

BIOPHARMACEUTICS

Question 4: Dimethaid proposes conducting a single-dose PK study to evaluate the systemic bioavailability of diclofenac from 2% gel for submission to the NDA, to be conducted in parallel to the (b) (4) Clinical Program. Does the Division agree?

FDA Response:

In principle, your proposed PK study design is acceptable. For approval of a 505(b)(2) application, the proposed PK study must use an approved/appropriate reference drug(s).

DISCUSSION:

The Sponsor stated that they will do a single-dose PK study using Voltaren® and Solaraze® as comparators. Dr. Rappaport stated that, although comparative bioavailability studies on all listed drugs relied upon would normally be required for 505(b)(2) applications, the Division would confirm its final position concerning the need to include Solaraze® in addition to Voltaren®. The Division's final position would be addressed in a post-meeting note. Dr. Lee suggested that, if the Sponsor is thinking of referencing Voltaren®, Solaraze®, and PENNSAID® 1.5% solution, the Sponsor should consider a three reference-arm study approach comparing Voltaren®/Solaraze®/PENNSAID® 1.5% solution to PENNSAID® Gel. The Sponsor questioned whether this approach would bridge the carcinogenicity information. Dr. Mellon stated that, if levels and exposure margins are equivalent then this would be acceptable. Dr. Mellon suggested that the Sponsor evaluate the information available in the Solaraze® label to see if they might be able to extrapolate information to their own label.

Post-Meeting comments:

From the pharmacology/toxicology perspective, if you plan on relying on the Agency's finding of safety for Solaraze®, a relative bioavailability study should be completed in order to establish the relevance of the dermal carcinogenicity data to your product and accurately describe the exposure margins for your product label.

CLINICAL QUESTIONS

Phase 1 Topical Safety Studies

Question 5: No additional topical safety studies are planned with the final to-be-marketed formulation. Does the Division agree?

FDA Response:

No. Dermal safety studies should be done on the to-be-marketed formulation. The solubility of the ingredients may affect safety. Even if the (b) (4) is not biologically active, if the gel formulation confines potential irritants to the surface longer, or to a more localized area, then this may increase the potential for irritation and sensitization.

In addition, the gel contains a higher concentration of diclofenac than the previous formulations. Although you note in your briefing package that there is a 3% diclofenac topical product (Solaraze® Gel) approved in the USA that "provides supportive evidence

that there are no anticipated local safety issues,”¹ it is for the treatment of actinic keratoses and has been evaluated for safety up to 90 days only. This does not constitute evidence that there are no anticipated local safety issues, since this product is meant to effect skin changes that result in eradication of the actinic keratoses, which may include killing and sloughing of the epidermal layers. Therefore, at least one dermal safety study will be required for the to-be-marketed formulation.

DISCUSSION:

The Sponsor stated that the gel formulation was the same as the solution with the exception of the (b) (4), which is an otherwise (b) (4) that is not expected to increase irritation or photosensitization. Dr. Okada stated her concern that, since the formulation is sufficiently different to affect the anticipated dosing regimen, the question remains whether the gel formulation could prolong contact of the DMSO excipient or higher concentration of diclofenac with the surface layers; therefore, the topical safety studies of the 1.5% formulation may not be adequate. The Sponsor stated that, since the topical safety studies performed with the 1.5% diclofenac solution were provocative and performed in conditions of supra-normal contact and topical exposure, the results of these studies should be sufficient to cover even the maximum clinical exposures that might be expected with the 2% gel formulation. The Sponsor felt that at this point, given that provocative topical safety studies provide only qualitative information as to whether irritation or photosensitization occurs, and given that quantitative information regarding application site adverse events exists from the studies of the 1.5% formulation, that additional topical safety studies would not be informative, but they would continue to actively monitor for these sorts of adverse events closely in the 2% diclofenac gel clinical studies. The Division acknowledged this rationale, but stated that additional internal discussion was needed to evaluate the adequacy and generalizability of the topical safety studies of the 1.5% diclofenac formulation for supporting the use of the 2% diclofenac gel formulation. The Division’s final position would be clarified in a post meeting note.

Post-Meeting comments:

When a change in formulation is being considered, such as lotion to gel, topical safety studies are generally required on the final to-be-marketed formulation, since the formulation of the vehicle can have an impact on safety and efficacy. Your 2% diclofenac gel contains a slightly higher concentration of diclofenac and a single different excipient (carbopol) than your 1.5% formulation. Your rationale for not performing topical safety studies on the 2% gel includes the fact that the 1.5% formulation topical safety studies were provocative and performed under supra-therapeutic conditions; that these qualitative results would not be expected to significantly differ for the 2% formulation because the products are so similar; that quantitative results (incidence of application site reactions) from the 1.5% clinical trials are expected to be similar given that the milligram dose of diclofenac and concentration of DMSO is the same for both formulations; and that skin reactions will be closely monitored and systematically assessed in the clinical studies of the 2% gel formulation. This rationale is reasonable; therefore, in this case, the Division will not require additional topical safety studies. However, your submission will need to include the data from the 1.5% PENNSAID®

¹ Further, we note that if you did intend to rely, in part, on the Agency’s finding of safety and/or effectiveness for Solaraze Gel (3% diclofenac sodium), you would need to identify this listed drug in accordance with the Agency’s regulations at 21 CFR §314.54.

topical safety studies and your rationale regarding the adequacy and generalizability of these data in supporting the clinical studies of the 2% gel.

(b) (4)

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/s/

Lauren Tornetta
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